ORIGINAL ARTICLE

Efficacy and safety of PD-L1 inhibitors versus PD-1 inhibitors in first-line treatment with chemotherapy for extensive-stage small-cell lung cancer

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Abstract

Objectives Programmed cell death-ligand 1 inhibitors plus chemotherapy (PD-L1 + Chemo) have achieved substantial progress in extensive-stage small-cell lung cancer (ES-SCLC). However, evidence about programmed cell death 1 inhibitors plus chemotherapy (PD-1 + Chemo) in SCLC is relatively lacking. Whether PD-1 inhibitors differ from PD-L1 inhibitors in their clinical outcomes remains controversial.

Materials and methods We performed a meta-analysis to compare efficacy and safety of PD-L1 + Chemo vs PD-1 + Chemo in ES-SCLC by searching PubMed, Embase, the Cochrane Library, and major oncology conferences. We examined overall survival (OS) as the primary outcome. Secondary outcomes included progression-free survival (PFS), objective response rate (ORR), and treatment-related adverse events (AEs).

Results We included four randomized trials (IMpower133, CASPIAN, KEYNOTE-604, and EA5161) with a total of 1553 patients. Direct comparison showed that PD-L1 + Chemo (PFS: hazard ratio [HR] 0.79; OS: HR 0.75) and PD-1 + Chemo (PFS: HR 0.72; OS: HR 0.77) significantly prolonged survival time compared with chemotherapy alone. But PD-L1 + Chemo (relative risk [RR]: 1.07) and PD-1 + Chemo (RR: 1.13) were not superior to chemotherapy alone in terms of ORR. Indirect comparison showed no significant difference in clinical efficacy between PD-L1 + Chemo and PD-1 + Chemo (OS: HR 0.99; PFS: HR 1.10; ORR: RR 0.95). We further stratified patients according to subgroups in terms of OS. In the subgroup of patients with brain metastasis, PD-L1 + Chemo tended to prolong OS (HR: 0.61, 0.28 to 1.32). There were no significant differences between PD-L1 + Chemo and PD-1 + Chemo regarding safety analyses. However, PD-L1 + Chemo exhibited a better safety profile in reducing the risk of treatment discontinuation due to AEs (RR: 0.43, 0.19 to 0.95) and pneumonia (pneumonia of any grade, RR: 0.59, 0.24 to 1.42; pneumonia of grade $\geq$ 3, RR: 0.37, 0.10 to 1.39).

Conclusions PD-L1 + Chemo and PD-1 + Chemo provided a significant survival benefit relative to chemotherapy alone for ES-SCLC. The efficacy and safety of PD-L1 + Chemo and PD-1 + Chemo were similar based on current evidence.

Keywords PD-L1 inhibitors · PD-1 inhibitors · Small-cell lung cancer · First-line therapy · Efficacy

Abbreviations

AEs	Adverse events
BBB	Blood-brain barrier
Chemo	Chemotherapy
CI	Confidence interval
DCs	Dendritic cells
ECOG	Eastern Cooperative Oncology Group
ESMO	European Society of Medical Oncology
HRs	Hazard ratios
IC	Immune cell
ICIs	Immune checkpoint inhibitors
irAEs	Immune-related adverse events
NCCN	National Comprehensive Cancer Network
NSCLC	Non-small-cell lung carcinoma
ORR	Objective response rate
OS	Overall survival
PD-1	Programmed cell death 1

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Précis: Our work confirmed that PD-L1+Chemo was not superior to PD-1+Chemo in terms of OS, PFS and ORR. However, PD-L1+Chemo tended to prolong OS for patients with brain metastases and exhibited a better safety profile relative to PD-1+Chemo.

Extended author information available on the last page of the article

PD-L1   Programmed cell death-ligand 1
PFS   Progression-free survival
RR   Relative risk
SE   Standard error
SCLC   Small-cell lung cancer
TC   Tumor cell
TMB   Tumor mutational burden

Background

Small-cell lung cancer (SCLC), a devastating carcinoma with rapid proliferation and early widespread metastases, accounts for 13–15% of all lung cancers [1]. The five-year survival rate for patients with extensive-stage SCLC (ES-SCLC) is as low as 1–2% treated with palliative chemotherapy [2]. For the past two decades, etoposide plus either cisplatin or carboplatin has been the standard first-line treatment for patients with ES-SCLC [3–5]. However, most patients rapidly develop resistance to chemotherapy [6], so more efficacious treatments are urgently needed.

The advent of the immunotherapy era provides us with new treatment options. The IMpower133 study shows that atezolizumab plus chemotherapy significantly prolonged overall survival (OS) (HR: 0.76; 95% CI: 0.60 to 0.95) and progression-free survival (PFS) (HR: 0.77; 0.63 to 0.95) compared to chemotherapy alone [7]. The CASPIAN study also demonstrates a synergetic antitumor effect and survival benefits with durvalumab plus chemotherapy [8]. Based on the results of these two studies, programmed cell death-ligand 1 inhibitor plus chemotherapy (PD-L1 + Chemo) has been approved in the USA and recommended by the National Comprehensive Cancer Network clinical practice guidelines as first-line treatment for patients with ES-SCLC (NCCN guidelines, http://www.nccn.org/professionals/). Prior to that, programmed cell death 1 inhibitors plus chemotherapy (PD-1 + Chemo) have shown promising antitumor activity for non-small-cell lung cancer (NSCLC) in several randomized controlled trials (RCTs) [9, 10], but data on PD-1 + Chemo in SCLC are relatively scarce.

The KEYNOTE-604 study has recently reported that pembrolizumab plus chemotherapy statistically improves PFS [11]. Meanwhile, a phase 2 RCT shows that nivolumab plus chemotherapy significantly prolongs both PFS and OS [12]. However, whether PD-L1 inhibitors and PD-1 inhibitors deliver similar efficacy and safety in combination with chemotherapy in ES-SCLC remains controversial.

In this meta-analysis, we aimed to assess the differences between PD-L1 + Chemo and PD-1 + Chemo in first-line treatment for ES-SCLC.

Method

Study eligibility

The PubMed, Embase, Cochrane Library, and major oncology conferences were searched for relevant studies, with main subject terms of "pembrolizumab" or "nivolumab" or "atezolizumab" or "durvalumab" or "tremelimumab" or "avelumab" or "immune checkpoint inhibitor" or "immune therapy" or "immunotherapy" or "programmed cell death protein-1" or "programmed cell death-ligand 1" or "PD-1" or "PD-L1," and "small-cell lung cancer" and "randomized controlled trial." The specific search strategy is shown in Supplemental Method. The major oncology conferences included the American Society of Clinical Oncology, the European Society of Medical Oncology, the American Association for Cancer Research, and the World Conference on Lung Cancer. Study selection was independently conducted by two investigators, and the decision was to be judged by the third investigators if there were any disagreements during the process.

Quality assessment

We assessed the risk of bias for the included RCTs (Supplementary Table 1). The specific criteria were as follows: (1) sequence generation, (2) allocation concealment, (3) blinding, (4) incomplete outcome data, (5) selective reporting, and (6) other source of bias.

Data extraction

The following information was extracted from each study to a standard sheet: (1) trial details (study ID, patient characteristics, treatment regimen, etc.); (2) the outcomes, namely OS, PFS, objective response rate (ORR), and adverse events (AEs). We extracted the hazard ratio (HR) and its 95% confidence intervals (CIs) for OS and PFS, and the relative risk (RR) for ORR and AEs.

Statistical analysis

We conducted direct comparison between immune checkpoint inhibitors (ICIs) plus chemotherapy and chemotherapy alone, and indirect comparisons between PD-L1 + Chemo and PD-1 + Chemo. In direct comparisons, the HRs of PFS and OS were pooled using the inverse-variance weighted method, while dichotomous data regarding ORR and AEs were pooled with the RR, 95% CIs and P values using the Mantel-Haenszel method. Statistical heterogeneity was determined by the χ^2 test and I^2 statistic: If $I^2 < 50\%$ or $P > 0.10$ in the χ^2 test indicated that significant heterogeneity did not exist, we used the fixed-effects model; otherwise, we used the random-effects model.

In indirect comparisons, we used frequentist methods with the following formula [13]: $\log HR_{AB} = \log HR_{AC} - \log HR_{BC}$, and its standard error (SE) for the log HR was $SE(\log HRAB) = \sqrt{SE(\log HRAC)^2 + SE(\log HRBC)^2}$. RR is calculated in a similar way. All statistical analyses were conducted using STATA (version 16.0).

Result

Characteristics of the eligible studies

This study included a total of four RCTs: Two explored the efficacy of anti-PD-L1 (atezolizumab or durvalumab) plus chemotherapy versus chemotherapy alone, and the other two explored the efficacy of anti-PD-1 (pembrolizumab or nivolumab) plus chemotherapy versus chemotherapy alone. The process of trial selection is shown in Supplementary Fig. 1. The main characteristics of the included RCTs and their outcomes are summarized in Table 1.

Direct comparisons of PD-L1/PD-1 inhibitors plus chemotherapy versus chemotherapy alone

In direct comparisons, patients receiving PD-L1 + Chemo exhibited significantly longer PFS ($HR_{PD-L1+Chemo/Chemo}$: 0.79, 95% CI: 0.68 to 0.90) and OS ($HR_{PD-L1+Chemo/Chemo}$: 0.75, 0.65 to 0.87) than patients receiving chemotherapy alone. Similar improvements of PFS ($HR_{PD-1+Chemo/Chemo}$: 0.72, 0.61 to 0.86) and OS ($HR_{PD-1+Chemo/Chemo}$: 0.77, 0.64 to 0.92) were observed with PD-1 + Chemo relative to chemotherapy alone (Figs. 1a and 1b). However, no significant difference in ORR was found when a PD-L1 inhibitor ($RR_{PD-L1+Chemo/Chemo}$: 1.07, 0.97 to 1.18) or a PD-1 inhibitor ($RR_{PD-1+Chemo/Chemo}$: 1.13, 1.00 to 1.28) was added to chemotherapy (Fig. 1c). In safety analyses, the frequency of treatment discontinuation due to adverse reactions was increased by adding a PD-1 inhibitor to chemotherapy ($RR_{PD-1+Chemo/Chemo}$: 2.33, 1.28 to 4.23) but not by adding a PD-L1 inhibitor ($RR_{PD-L1+Chemo/Chemo}$: 1.00, 0.59 to 1.70). However, relative to chemotherapy, neither PD-1 + Chemo nor PD-L1 + Chemo was associated with significant differences in the frequency of AEs of any grade, AEs of grade ≥ 3, and treatment-related death (Figs. 2a and 2b).
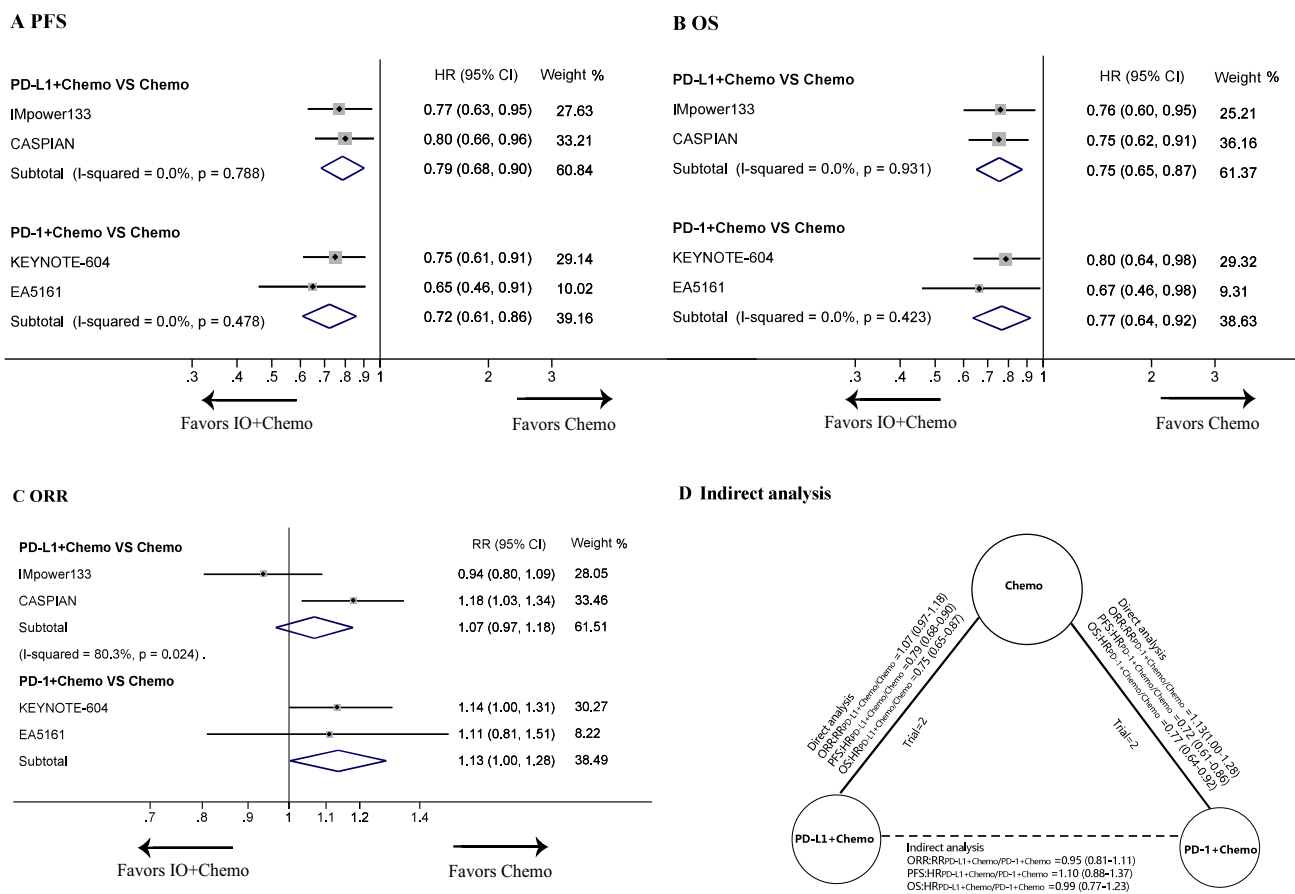
Indirect comparisons between PD-L1 + chemo versus PD-1 + chemo

Indirect comparisons showed that PD-L1 + Chemo was comparable with PD-1 + Chemo in terms of OS ($HR_{PD-L1+Chemo/\ PD-1+Chemo}$: 0.99, 0.77 to 1.23), PFS ($HR_{PD-L1+Chemo/\ PD-1+Chemo}$: 1.10, 0.88 to 1.37), and ORR ($RR_{PD-L1+Chemo/\ PD-1+Chemo}$: 0.95, 0.81 to 1.11) (Fig. 1d). Analyses of AEs suggested that the overall incidence

Table 1 Characteristics of patients and outcomes of included trials

Trial name	Arm	N	Median age	Males (%)	Smoke (%)	ECOG1 (%)	Brain metastases (%)	ORR (%)	Follow-up (m)	OS (m)	PFS (m)	HR for PFS 95%CI	HR for OS 95%CI
IMpower133	Atezolizumab+chemotherapy	201	64	64.2	95.5	63.7	8.5	60	22.9	12.3	5.2	0.77 (0.63–0.95)	0.76 (0.60–0.95)
	chemotherapy	202	64	65.3	98.5	66.8	8.9	64	22.9	10.3	4.3	Ref	Ref
CASPIAN	Durvalumab+chemotherapy	268	62	71	92	63	10	68	25.1	12.9	5.1	0.80 (0.66–0.96)	0.75 (0.62–0.91)
	chemotherapy	269	63	68	94	67	10	58	25.1	10.5	5.4	Ref	Ref
KEYNOTE-604	Pembrolizumab+chemotherapy	228	64	66.7	96.5	73.7	14.5	71		10.8	4.5	0.75 (0.61–0.91)	0.80 (0.64–0.98)
	chemotherapy	225	65	63.1	96.4	75.1	9.8	62		9.7	4.3	Ref	Ref
EA5161	Nivolumab+chemotherapy	80						52		11.3	5.5	0.65 (0.46–0.91)	0.67 (0.46–0.98)
	chemotherapy	80						48		8.5	4.6	Ref	Ref

N Number; *ECOG* Eastern Cooperative Oncology Group; *ORR* Objective response rate; *HR* Hazard ratio; *PFS* Progression-free survival; *OS* Overall survival; *Ref:* Reference

A PFS

B OS

C ORR

D Indirect analysis

Fig. 1 Direct and indirect comparisons between PD-L1 inhibitors plus chemotherapy (PD-L1 + Chemo) or PD-1 inhibitors plus chemotherapy (PD-1 + Chemo) with chemotherapy alone. Figure **a**, **b**, and **c** showed the forest plot of hazard ratios (HRs) and risk ratios (RRs) directly comparing progression-free survival (PFS), overall survival (OS), and objective response rate (ORR) between PD-L1 + Chemo or PD-1 + Chemo with chemotherapy. The solid lines of Figure **d** represent the existence of direct comparisons between the treatments, whereas the dashed line represents the indirect comparison between

PD-L1 + Chemo versus PD-1 + Chemo. The size of the circle corresponds to the number of enrolled patients. The horizontal line crossing the square represents the 95% CI. The diamonds represent the estimated overall effect, based on the meta-analysis. All statistical tests were two-sided. Abbreviations: IO, immuno-oncology; PD-L1, programmed cell death-ligand 1; PD-1, programmed cell death 1; Chemo, chemotherapy; HR, hazard ratio; RRs, risk ratios; CI, confidence interval

of toxicity was similar between PD-L1 + Chemo and PD-1 + Chemo (Fig. 2c). However, the rate of drug discontinuation due to AEs was lower in patients receiving PD-L1 + Chemo ($RR_{PD-L1+Chemo/ PD-1+Chemo}$: 0.43, 0.19 to 0.95). A trend toward reduced risk of pneumonia was also observed in the PD-L1 + Chemo group (pneumonia of any grade, $RR_{PD-L1+Chemo/ PD-1+Chemo}$: 0.59, 0.24 to 1.42; pneumonia of grade ≥ 3, $RR_{PD-L1+Chemo/ PD-1+Chemo}$: 0.37, 0.10 to 1.39).

Subgroup analysis for OS

Subgroup data were available in three studies: IMpower133, CASPIAN, and KEYNOTE-604. Analyses by gender, age, performance status, and brain metastasis status are shown in Fig. 3.

When compared PD-L1 + Chemo or PD-1 + Chemo with chemotherapy, a consistent OS benefit was seen across most of the specified subgroups except for the subgroup based on brain metastasis status at baseline. For patients without brain metastases, both PD-L1 + Chemo ($HR_{PD-L1+Chemo/ Chemo}$: 0.74, 0.63 to 0.87) and PD-1 + Chemo ($HR_{PD-1+Chemo/ Chemo}$: 0.75, 0.60 to 0.94) were superior to chemotherapy. For patients with brain metastases, PD-L1 + Chemo revealed a superior trend ($HR_{PD-L1+Chemo/ Chemo}$: 0.80, 0.49 to 1.31) while PD-1 + Chemo revealed an inferior trend ($HR_{PD-1+Chemo/ Chemo}$: 1.32, 0.72 to 2.42) relative to chemotherapy alone. Thus, PD-L1 + Chemo tended to reduce the risk of death relative to PD-1 + Chemo ($HR_{PD-L1+Chemo/ PD-1+Chemo}$: 0.61; 0.28 to 1.32).

AEs

A.PD-L1+Chemo VS Chemo   **RR (95% CI)**

Grade≥3	0.99 (0.90−1.10)
Any grade	1.02 (0.99−1.05)
Leading to discontinuation	1.00 (0.59−1.70)
Leading to death	0.89 (0.46−1.72)
Any grade pneumonia	0.61 (0.30−1.27)
3−5 grade pneumonia	0.55 (0.19−1.64)

Favors PD-L1+Chemo   Favors Chemo

B.PD-1+Chemo VS Chemo

Grade≥3	1.02 (0.92−1.14)
Any grade	1.00 (0.99−1.02)
Leading to discontinuation	2.33 (1.28−4.23)
Leading to death	1.17 (0.55−2.47)
Any grade pneumonia	1.04 (0.62−1.74)
3−5 grade pneumonia	1.50 (0.69−3.27)

Favors PD-1+Chemo   Favors Chemo

C.PD-L1+Chemo VS PD-1+Chemo

Grade≥3	0.97 (0.84−1.12)
Any grade	1.02 (0.99−1.05)
Leading to discontinuation	**0.43 (0.19−0.95)**
Leading to death	0.76 (0.28−2.10)
Any grade pneumonia	0.59 (0.24−1.42)
3−5 grade pneumonia	0.37 (0.10−1.39)
irAEs	1.40 (0.28−7.17)

0   0.5   1   1.5   2   2.5   3   3.5   4

Favors PD-L1+Chemo   Favors Chemo
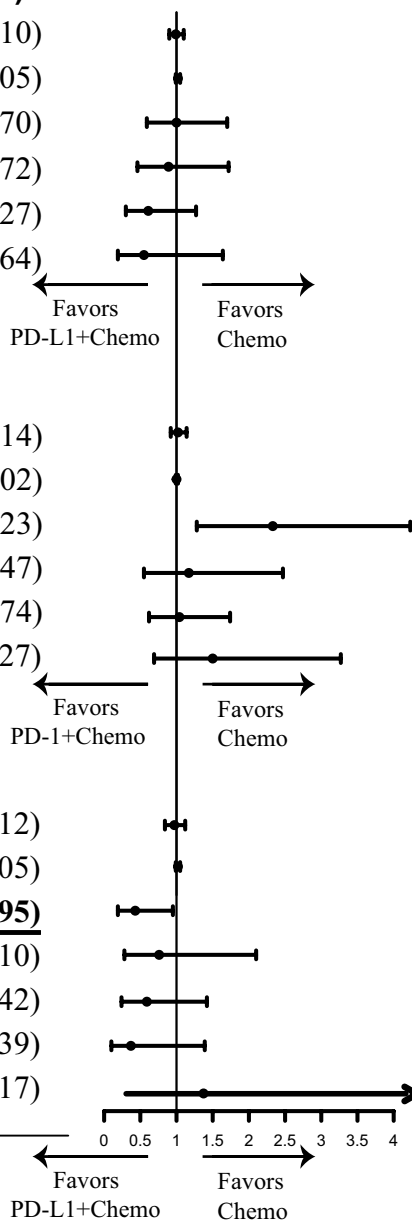
Fig. 2 Direct and indirect comparisons of safety among PD-L1+Chemo, PD-1+Chemo, and chemotherapy. The forest plots of risk ratios (RRs) for safety comparing PD-L1+Chemo with chemotherapy, PD-1+Chemo with chemotherapy, and PD-L1+Chemo with PD-1+Chemo were shown in Figure **a**, **b,** and **c**, individually. The horizontal line crossing the dot represents the 95% CI. All statistical tests were two-sided. Abbreviations: PD-L1, programmed cell death-ligand 1; PD-1, programmed cell death 1; Chemo, chemotherapy; AEs, adverse events; irAEs, immune-related adverse events; RR, risk ratio

Discussion

To our knowledge, this is the first meta-analysis to specifically investigate the differences between PD-L1+Chemo and PD-1+Chemo in patients with ES-SCLC. The study demonstrated that PD-L1+Chemo is comparable to PD-1+Chemo in terms of OS, PFS, and ORR as first-line treatment for ES-SCLC. However, PD-L1+Chemo revealed an advantage in the safety profile, with a significantly lower risk of treatment discontinuation caused by AEs, as well as a numerically lower risk of pneumonia compared with PD-1+Chemo.
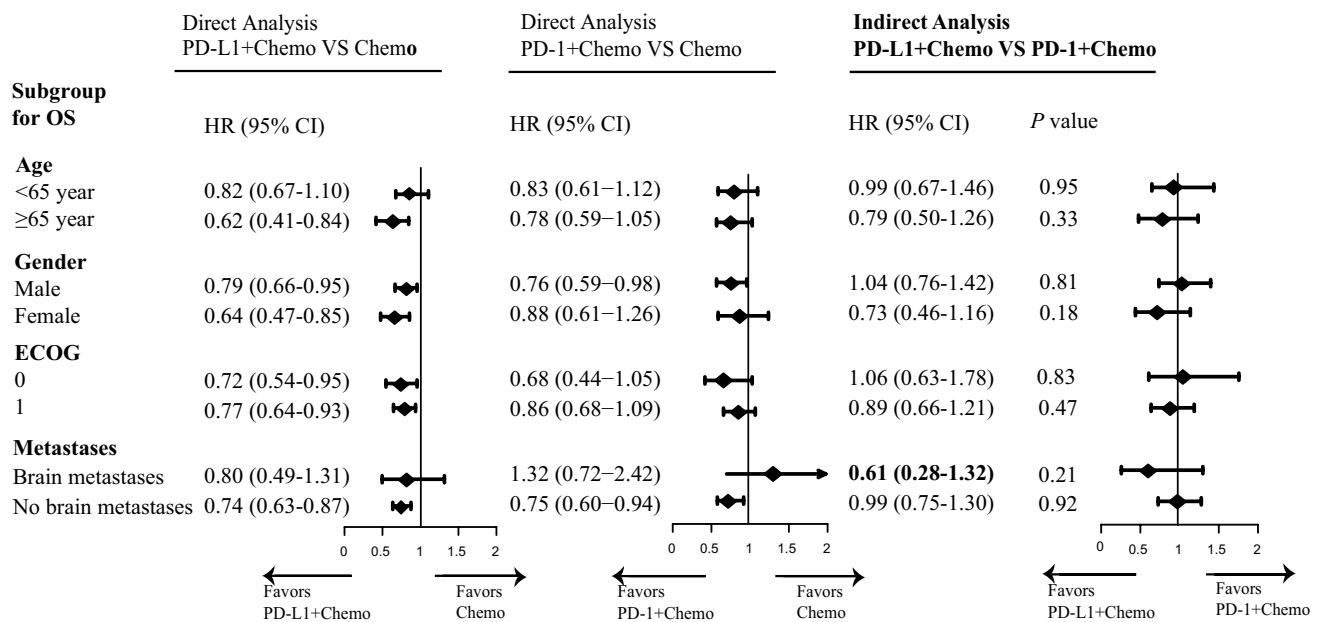
Fig. 3 Subgroup analyses for overall survival in treatment of extensive-stage small-cell lung cancer. Subgroups including gender, age, performance status, and brain metastasis status were analyzed. The forest plots of hazard ratios (HRs) for OS comparing PD-L1+Chemo with chemotherapy, PD-1+Chemo with chemotherapy, and PD-L1+Chemo with PD-1+Chemo were shown in the left, middle, and right column, individually. The horizontal line crossing the dot represents the 95% CI. All statistical tests were two-sided. Abbreviations: PD-L1, programmed cell death-ligand 1; PD-1, programmed cell death 1; Chemo, chemotherapy; HR, hazard ratio

Differences between the clinical performance of PD-L1 inhibitors and PD-1 inhibitors have been reported in several studies. A published meta-analysis has shown that the risk of death is significantly reduced for patients treated with PD-1+Chemo compared with PD-L1+Chemo in NSCLC ($HR_{PD-1+Chemo/ PD-L1+Chemo}$: 0.66, 0.48 to 0.90) [14]. The underlying mechanism remains to be fully elucidated but one possible reason may be that the interaction of PD-1 and PD-L2 may also inhibit the activation of T cells. And as we know, the PD-1 inhibitor could block the binding of PD-1 to both PD-L1 and PD-L2, while the PD-L1 inhibitor could inhibit only the binding of PD-1 to PD-L1. Thus, the tumor might escape antitumor immune response through the PD-1/PD-L2 axis when being treated with PD-L1 inhibitor [15]. However, for SCLC, our results showed no significant difference between PD-L1+Chemo and PD-1+Chemo in terms of OS ($HR_{PD-L1+Chemo/ PD-1+Chemo}$: 0.99, 0.77 to 1.23) and PFS ($HR_{PD-L1+Chemo/ PD-1+Chemo}$: 1.10, 0.88 to 1.37). And the results were consistent with another analysis performed by other method (Bayesian approach) [16]. The potential explanation could be that SCLC and NSCLC differ in their immune microenvironment, e.g., PD-L1 expression is typically low or absent in SCLC [17]. Another possible explanation is that PD-L1 binds two receptors, PD-1 and B7.1 (CD80), and B7.1 on tumor-associated dendritic cells (DCs) is a key costimulatory molecule to enhance T cell priming by B7.1/CD28 interaction. Thus, PD-L1 inhibitors play more

roles than PD-1 inhibitors to relieve B7.1 by blocking PD-L1 on DCs, which further reinvigorates DCs function and help initiate anticancer T cell immunity [18].

However, the underlying mechanisms of differences between PD-L1 inhibitors and PD-1 inhibitors in SCLC remain to be investigated with well-defined animal models. Currently, it is clinically relevant to assess predictive biomarkers for PD-L1 inhibitors versus PD-1 inhibitors when combined with chemotherapy in SCLC. Although expression of PD-L1 has been considered as a potential predictive biomarker of response to ICIs in various cancer types, the reliability of PD-L1 expression in predicting efficacy of PD-L1/PD-1+Chemo in SCLC is poor [7, 11]. For one reason, the biopsy samples from SCLC are often small and dominated by necrotic area. In the data of PD-L1 expression form study IMpower133, only 137 had evaluable tissue material in the all 403 patients enrolled, which reflected the difficulties in obtaining biopsy material [7]. For another reason, PD-L1 in SCLC is mainly expressed on tumor-infiltrating immune cell (IC), but not tumor cell (TC), which is different from NSCLC [19]. These suggest that PD-L1 expression may not be a perfect predictive biomarker for SCLC patients receiving PD-L1+Chemo or PD-1+Chemo. Tumor mutational burden (TMB) is another characteristic of the immune microenvironment for SCLC. However, among the four trials enrolled, the predictive value of TMB was only analyzed in IMpower133 and could not be pooled.

More data are warranted to unveil the value of blood TMB or tissue TMB in SCLC. Other biomarkers, including but not limited to tumor microenvironment, gut microbiomics, and host immune status should be also studied in the future.

In subgroup analysis, there was a tendency to reduce the risk of death in patients with brain metastases for receiving PD-L1 + Chemo than PD-1 + Chemo ($HR_{PD-L1+Chemo/ PD-1+Chemo}$: 0.61; 0.28 to 1.32). However, the result should be interpreted with caution because of the small population size for this subgroup in KEYNOTE-604. While the mechanisms behind the difference performance of PD-1 inhibitors versus PD-L1 inhibitors in patients with brain metastasis are unknown. Essential steps are urgently needed to explore the mechanism from the following aspects, including a prospective study to confirm this finding; more knowledge about the tumor microenvironment of brain metastases in SCLC; the difference of the ability to penetrate the bloodbrain barrier (BBB) between PD-L1 and PD-1 inhibitors.

As for safety, although there were no significant differences between PD-L1 + Chemo and PD-1 + Chemo for AEs of any grade, receiving PD-L1 + Chemo was associated with lower risk of treatment-related drug discontinuation. This might be related to the ability PD-L1 inhibitors of preserving normal immunological homoeostasis by retaining its programmed cell death-ligand 2. A previous study also revealed the best safety profile of atezolizumab in various cancers [20]. And the result suggests that PD-L1 + Chemo might have an advantage in reducing specific AEs such as pneumonia. Our results revealed that PD-L1 + Chemo tended to reduce incidence of pneumonia, compared with PD-1 + Chemo (pneumonia of any grade, $RR_{PD-L1+Chemo/ PD-1+Chemo}$: 0.59, 0.24 to 1.42; pneumonia of grade $\geq$ 3, $RR_{PD-L1+Chemo/ PD-1+Chemo}$: 0.37, 0.10 to 1.39). This was consistent with the previous finding that PD-1 inhibitors may increase the rate of pneumonia with NSCLC patients compared with PD-L1 inhibitors [21].

Although our study demonstrated that the clinical effects of PD-1 + Chemo and PD-L1 + Chemo were similar, the use of PD-1 + Chemo in the first-line treatment for ES-SCLC should be undertaken with caution for two reasons: In the EA5161 study, OS was a secondary endpoint, which does not meet the standard approved by the US Food and Drug Administration, and there has been no prospective head-to-head comparison between PD-L1 + Chemo and PD-1 + Chemo. Unfortunately, such a prospective study will probably not be done, which makes this indirect comparison important to meet current clinical requirements. The results of our study provide evidence to support the treatment choice for the application of PD-1 + Chemo in SCLC.

In conclusion, based on the present limited data, this study indicated that PD-L1 + Chemo and PD-1 + Chemo had no statistically significant differences in OS, PFS, and ORR for ES-SCLC. However, PD-L1 + Chemo exhibited a statistically better safety profile in reducing the risk of treatment discontinuation due to AEs and pneumonia.

Declarations

Conflict of interest The authors declare that they have no competing interests.

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